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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/050,902	01/18/2002	Wolfgang A. Renner	1700.0190004/BJD/SJE	7792

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EXAMINER	
MOSHER, MARY	
ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 03/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/050,902	RENNER ET AL.	
	Examiner	Art Unit	
	Mary E. Mosher, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-218* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,100,135,175 and 176* is/are rejected.

7)☐ Claim(s) *2-11,13-35,43-49,86,101-105,108,121-134,136-156,173,174,177-179,185-189 and 198* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *See continuation*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 12,36-42,50-85,87-99,106,107,109-120,157-172,180-184,190-197 and 199-218.

Continuation of Attachments 3: PTO-1449s: 11/13/02, 11/21/02, 11/26/02, 3/14/03, 8/19/03, 9/15/03, 10/29/03

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group I, species core = Qβ, antigen = VEGFR, and connection = sulfhydryl + amino groups, in Paper No. 9/26/2003 is acknowledged. The traversal is on the ground(s) that search for one species should find art relevant to all the other species, and that search for group I should find art relevant for group II. This is not found persuasive because group II requires search of specific structures that are not required for group I, and because the claimed lists of species of core, linker, and antigen include a large number of very different products, and the different products require divergent search.

The requirement is still deemed proper and is therefore made FINAL.

Claims 12, 36-42, 50-85, 87-99, 106, 107, 109-120, 157-172, 180-184, 190-197, and 199-218 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected group and/or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9/26/2003.

Claims 1-11, 13-35, 43-49, 86, 100-105, 108, 121-156, 173-179, 185-189, 198 have been examined to the extent that they read upon the elected species, except as noted below.

Claim Objections

Claims 1-11, 13-35, 43-49, 86, 100-105, 108, 121-156, 173-179, 185-189, 198 are objected to because they are not limited to the elected invention.

Specification

The disclosure is objected to because of the following informalities: the specification and claims are not in full compliance with the Sequence Rules, 37 CFR 1.821-1.825. There are sequence recitations without accompanying SEQ ID numbers, see e.g. Example 18 in the specification and claim 49. Applicant should review the entire specification for compliance with the Sequence rules.

Appropriate correction is required.

Search of the elected combination indicates that it is free of the art, because the prior art does not provide particular direction to combine a VEGFR2 antigen with a particle of Qβ. Applicant's finding that the particle-presented VEGFR2 antigen could break self-tolerance is also noted. Li et al (Current Molecular Medicine 3:773-779, 2003, not prior art) provides evidence substantiating applicant's assertions that an immune response induced against VEGRF can be useful in cancer immunotherapy. Therefore in accordance to MPEP 803.02, search and examination was extended to the generic and/or linking claims 1, 100, and 135.

Claim Rejections - 35 USC § 112

Claims 1, 100, 135, and 176 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 135 recite "a virus-like particle comprising recombinant proteins, or fragments thereof, of a bacteriophage." It is not clear if the claims require the particle to resemble a bacteriophage. For example, if a recombinant hepatitis B particle comprised

a 2-amino acid sequence which happened to occur in some M13 gene product, this literally would be a virus-like particle comprising a fragment of a recombinant protein of a bacteriophage. Is this the intent? To clarify the claims, changing "virus-like" to "bacteriophage-like" is suggested.

In addition, claim 100 recites "a self antigen". This is unclear, because any antigen which is "self" to one organism is "nonself" to another, e.g. human VEGRF2 is a self antigen to a human but nonself to a rabbit. The metes and bounds of the claimed subject matter are indefinite, because the claim does not indicate who or what the "self" is.

Claim 176 is confusing in that it recites "the vaccine composition of claim 160", but claim 160 is not drawn to a vaccine. In the interest of compact prosecution, the examiner assumes that this claim is meant to depend from claim 175. However, correction is required.

Claims 175-176 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. These claims are drawn to a vaccine composition. The conventional meaning of the term "vaccine" is a material which induces an immune response that protects the host from a disease. The specification teaches that the elected species is able to induce an immune response against mouse VEGFR2 in mice, and subsequent work by others substantiates applicant's assertions that an immune response against VEGRF2 is

useful in treating cancer. However, the specification provides no evidence that immunization with the VEGFR2 particle will prevent disease, and it is not well established in the cancer art that immunological methods are effective in prevention. In addition, neither the specification nor the art published to date indicates whether or not there are any long-term effects of creating an autoimmune reaction directed against VEGFR2 in an undiseased host. Considering the state of the art, the lack of a working example, and the limited guidance in the specification, it is concluded that undue experimentation would be required to enable the claimed vaccine.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 135 are rejected under 35 U.S.C. 102(b) as being anticipated by Mastico et al US 5,698,424. Mastico teaches a particle made of modified recombinant bacteriophage protein, and either a peptide or an enzyme covalently linked to the modified site in the particle by a non-peptide bond, see columns 7 and 8 for example. Mastico also teaches that the particles present epitopes in a regular array, see column 4, lines 21-36 for example. Therefore, the reference meets each and every limitation for these generic and/or linking claims.

Claim 100 is rejected under 35 U.S.C. 102(e) as being anticipated by Schiller et al US 2002/0081295. Schiller teaches a mouse TNF-α arrayed on a virus-like particle

via a nonpeptide bond, and teaches induction of autoimmunity in a mouse.See pages 7-8, paragraphs 046-051. This meets each and every limitation of this generic and/or linking claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 100 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Chackerian et al (Proceedings of the National Academy of Sciences USA 96:2373-2378, 1999) and Renner et al WO 00/32227. Chackerian teaches a particle displaying a repetitive array of a mouse self-antigen peptide, and broadly teaches this sort of particle as able to induce antibodies against self-antigens. This differs from the claim only in that the reference teaches a peptide bond between the core particle and the antigenic determinant, and the claim specifies a non-peptide bond. Renner teaches immunogenic particles displaying repetitive antigens linked to the particle by nonpeptide bonds, see for example pages 8 and 9. This differs from the claim only in that Renner does not teach a self-antigen. Renner and Chackerian both teach human papillomavirus particles as platforms to repetitively display antigens. It

would have been within the ordinary skill of the art to modify the teachings of Chackerian by using the alternative links taught by Renner, and it would have been within the ordinary skill of the art to modify the teachings of Renner by choosing a self-antigen for presentation as taught by Chackerian, with reasonable expectation of success. The invention as a whole is therefore prima facie obvious, absent unexpected results.

Allowable Subject Matter

The subject matter of claims 1-11, 13-35, 43-49, 86, 100-105, 108, 121-156, 173, 174, 177-179, 185-189, 198 would be allowable if limited to a bacteriophage-like particle associated through a nonpeptide bond to VEGFR2 or an antigenic determinant thereof, where the particle presents VEGFR2 (or its determinant) in an ordered and repetitive array.

The following is a statement of reasons for the indication of allowable subject matter: Schiller and Chackerian broadly teach that immune tolerance to a self-antigen can be broken by administering the antigen in the form of a repetitive array, e.g. by presentation on a virus-like particle. Schiller explicitly suggests using an RNA phage virus-like particle, see page 9, paragraph 0054, and suggests proteins associated with angiogenesis as self-antigens for use, see page 4, paragraph 0023. However, in the peer-reviewed publication, Chackerian indicates that "It remains to be determined what specific features of these arrays are critical and how the spacing of self-antigen effects autoantibody production." Prior art such as Witte et al (Cancer and Metastasis Reviews 17:155-161, 1998) teaches that passive immunotherapy using anti-VEGFR2 antibody

was effective in cancer treatment. However, the prior art is silent upon the whether or not active immunity against VEGFR2 can be induced, and upon whether or not active immunity would be effective in cancer treatment. Considering the uncertainty for generally breaking self-tolerance by changing the repetitive array from a human papillomavirus particle to a bacteriophage particle, and the uncertainty of success for inducing VEGFR2 autoimmunity, the prior art at best suggests the above invention as obvious to try.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary E. Mosher, Ph.D. whose telephone number is 571-272-0906. The examiner can normally be reached on M-T and alternate F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

2/25/04

MARY E. MOSHER
PRIMARY EXAMINER
GROUP ~~1800~~ 1600